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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,669	09/21/2001	Jean-Louis Ruelle	BM45339	9875

25308 7590 07/15/2003

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EXAMINER	
BASKAR, PADMAVATHI	
ART UNIT	**PAPER NUMBER**
1645	12

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/857,669	Applicant(s) RUELLE, JEAN-LOUIS	
	Examiner Padmavathi v Baskar	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-59,61 and 63-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-58, 61, 63-68* is/are rejected.

7)☒ Claim(s) *59* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendment

1. The amendment filed on 3/24/03 has been entered into the record. Claims 60 and 62 have been canceled. Claims 55 and 59 have been amended. New claims 63-68 have been added. Claims 55-59, 61 and 63-68 are pending in the application.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

3. The Examiner acknowledges the various amendments to the specification in response to Specification informalities as cited in the previous office action.

Rejection Withdrawn

4. In view of amendment to the claim 55 and cancellation of claim 62, the rejection under 35 U.S.C. 112, second paragraph is withdrawn.

Rejection maintained.

5. The rejection of claims 55, 56 and 61 under 35 U.S.C. 102(a) as being anticipated by Martin et al 1997 (J.Ex.Med. Volume 185, Number 7, April 7, 1997 1173-1184) is maintained as set forth in the previous office action.

Claims are directed to an isolated polypeptide comprising a member selected from the group consisting of an amino acid sequence SEQ.ID.NO: 2

Claims are also directed to an immunogenic composition comprising said polypeptide and a pharmaceutically acceptable carrier.

Martin et al disclose an isolated polypeptide from whole cell lysate of outer membrane protein (OM) preparations (page 1174, under materials and method, antigens) from N.meningitidis. Monoclonal antibodies were produced in mice with OM preparation indicating that the disclosed isolated polypeptide preparation is immunogenic. The antigen to which an immune response has to be elicited is in general in a hydrophilic phase (i.e., buffer). Therefore,

the examiner is considering this preparation as an immunogenic composition. Whole cell lysates prepared in buffer (i.e., pharmaceutical carrier) from N.meningitidis inherently comprise SEQ.ID.NO: 2 See (In re Horvitz, 168 F 2d 522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948). Since the Office does not have the facilities for examining and comparing applicants' product with the product of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicants' arguments filed on 3/24/03 have been fully considered but they are not deemed to be persuasive.

Applicant states that Martin et al does not disclose the claimed isolated polypeptide and cites MPEP 2131.

It is the examiner's position that there is no evidence on the record to show that the claimed polypeptide was not inherently disclosed by Martin et al. Applicant has not shown any side-by-side comparison of applicant's product with the product of prior art to obviate the rejection. Further, the limitation "comprising" in the claim does not limit the invention to an isolated polypeptide "SEQ.ID.NO: 2 " and inherently contains many other polypeptides. Applicant's attention is drawn to claim 59. This claim is not rejected under 102 (b) since the scope of the claim is limited to SEQ.ID.NO: 2. However, the scope of the invention in claims 55, 56 and 61 is not limited to SEQ.ID.NO: 2. Therefore, this rejection is maintained.

New Claim Rejections - 35 U.S. C. 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, cl ar, concise, and exact terms as to nable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 55-58, 61 and 63-68 are rejected under 35 U.5.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the interim guidelines on written description published June 15, 1998 in the Federal Register at Volume 63, Number 114, pp 32639-32645 (also available at www.uspto.gov). This is a written description rejection.

The claims are drawn to an isolated polypeptide comprising SEQ.ID.NO: 2 and an immunogenic fragment comprising at least 15 amino acids or 20 amino acids. Claims are also drawn to fusion protein and immunogenic compostion comprising said fragments, pharmaceutically acceptable carrier and adjuvant.

The specification broadly describes as part of the invention, an isolated protein of SEQ ID NO: 2, which is encoded by BASB040 gene from N.meningitidis, ATCC strain 13090. The specification also teaches on page 59 that this full-length protein contains 609 amino acids. However, the specification does not teach fragments or immunogenic composition or fusion protein comprising said fragments (i.e., 15 amino acids or 20 amino acids.)

The actual biological function of the protein represented as SEQ ID NO: 2 is not set forth in this specification. Applicants broadly describe the invention as embracing any deletion by use of language in which a specified percent of amino acids can be changed in the protein. USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The inv ntion is, for purposes of the 'written description' inquiry, whatever is now claimed." (See

page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116).

Thus, an isolated polypeptide consisting of SEQ ID NO: 2 meets the written description provision of 35 U.S.C. 112, first paragraph for the reasons set forth below.

The specification fails to teach an isolated polypeptide fragments of SEQ ID NO: 2 and it is noted that the claimed fragments do not exist as an invention independent of their function in encoding a protein, SEQ.ID.NO: 2. The actual structure or other relevant identifying characteristics of each protein fragment having the claimed properties of the protein can only b determined empirically by actually making every nucleic acid that encodes the recited fragments and testing each to determine whether such a fragment having the particularly disclosed properties of full length protein. For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonable predict the complete structure of the claimed invention from its function. This specification does not teach such, and the art is devoid of this correlation for SEQ ID NO: 2 protein with undetermined function. There is no written description support for an isolated fragments comprising 15 amino acids or 20 amino acids or immunogenic composition or fusion protein comprising said fragments as claimed.

The isolated polypeptide comprising of SEQ ID NO: 2 is uncharacterized by this specification and is not asserted to belong to any known family of proteins. The specification fails to teach the structure or relevant identifying characteristics of a representative number of SEQ.ID.NO: 2 fragments, sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 U5PQ2d 1601, 1606 (CAFC 1993) and Amgen Inc V Chuaai

Pharmaceutical Co Ltd., 18 U5PQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 U5PQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

8. Claims 55-58, 61 and 63-68 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide consisting of SEQ ID NO: 2 or immunogenic composition comprising the isolated polypeptide of SEQ ID NO: 2 and a pharmaceutically accepted carrier and an adjuvant, the specification does not reasonably provide enablement for any isolated polypeptides comprising an immunogenic fragments of SEQ.ID.NO: 2, wherein said immunogenic fragments comprising at least 15 amino acids or 20 amino acids, fusion protein comprising said polypeptide or said fragments and a polypeptide selected to: provide T-helper epitopes, facilitate purification from recombinant expression system or stabilize the isolated polypeptide during recombinant expression. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims since ther is no written description support for the claimed invention.

These claims are not enabled for the following reasons: The written description is limited to only SEQ ID NO: 2 and is described as an isolated polypeptide, SEQ ID NO: 2, which is encoded by BASB040 gene from N.meningitidis, ATCC strain 13090. The specification also teaches on page 59 that this full-length polypeptide, SEQ.ID.NO: 2 consist of 609 amino acids. The specification fails to teach that the claimed antigenic fragments are detected by immune sera and further lacks any description of any such fragments. The specification is silent in teaching fusion proteins as claimed. The specification is not enabled for any fragments of SEQ ID NO: 2 because 1) the specification fails to teach fragments that are able to function by binding to immune s ra; 2) the sp cification fails to t ach how to make and use fragments

thereof that have an unknown and uncharacterized function; 3) the specification fails to teach what are the critical amino acid residues that can be modified and still achieve a fragment with functional activity 4) the art teaches that proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, one skilled in the art would have reason to doubt the validity and functionality of the function of such antigenic fragments of SEQ ID NO:2, and 5) applicants have not displayed a nexus between the structure and function of the claimed fragments. As to points 1)- 5), the specification fails to provide a written description of any fragments of a bacterial protein sequence of SEQ ID N0: 2. The specification fails to teach the critical protein residues involved in the function of the protein SEQ ID NO: 2, such that the skilled artisan is provided no guidance to test, screen or make fragments of the protein comprising SEQ ID NO: 2. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid

substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of a single amino acid residue may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol, 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis in proteins and such proteins differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition. Applicants have not taught which residues of SEQ ID NO: 2 can be varied and still achieve a protein that is functional. Since, the specification lacks a written description of any fragment of SEQ ID NO: 2, it is not enabled for this language because it fails to enable the skilled artisan to envision the detailed chemical structure of the claimed variants or fragments of SEQ.ID.NO: 2 as well as how to use the claimed antigenic fragments of SEQ ID NO: 2 and fusion protein as claimed. The skilled artisan would be forced into undue experimentation to make and use the instantly claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 61 and 63-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martin et al 1997 (J.Ex.Med. Volume 185, Number 7, April 7, 1997 1173-1184) as applied above in paragraph # 5 and further in view of Prieels et al WO/9400153.

Claims are drawn to an immunogenic composition comprising SEQ.ID.NO: 2, carrier, oil-in-water emulsion, aluminum salt and TH1 type adjuvant 3D –MPL and QS21

Martin et al as explained above do not teach carrier, oil-in-water emulsion, aluminum salt and TH1 type adjuvant 3D –MPL and QS21

1. Prieels et al WO/9400153 teach the importance of safe and efficacious TH1 type adjuvants such as 3D –MPL and QS21 (see page 14 and claims), and carriers oil-in-water emulsion (see page 5, last three lines) or alum salt in recombinant or peptide based vaccine preparations for human use. Recombinant or peptide antigens, while providing specific and appropriate epitopes for immune recognition, are intrinsically poor immunogens. Therefore, appropriate adjuvants 3D –MPL and QS21 for optimal protection has been suggested (pages 2-4). It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use adjuvants such as 3D –MPL and QS21 for developing effective vaccine preparations. An artisan of ordinary skill would have been motivated in applying the teaching of Martin et al to Prieels et al with a reasonable expectation of success because Martin et al teach isolated polypeptides and Prieels et al teach adjuvant like 3D –MPL and QS21 in recombinant vaccine preparations. The claimed invention is prima facie obvious in view of Martin et al and Prieels et al absent any convincing evidence to the contrary.

12. Claim 59 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Status of Claims

13. No claims are allowed.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma Baskar whose telephone number is (703) 308-8886. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4 PM EST

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Padma Baskar Ph.D.

7/8/03

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice of References Cited

Application/Control No.	Applicant(s)/Patent Under Reexamination	
09/857,669	RUELLE, JEAN-LOUIS	
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U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	WO 94/00153	01-1994	Europe	Prieels	
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6
	V	Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990
	W	Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988
	X	Jobling et al. Mol. Microbiol, 1991, 5(7): 1755-67

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.